

# Elevated Erythropoietin and Multicystic Neoplasm of the Pancreas

Qiang Nai Kalyani Regeti Sabrina Arshed  
Mohammed Amzad Hossain Ping Zhang Hongxiu Luo Shilpi Singh  
Teena Mathew Mohammed Islam Shuvendu Sen Abdalla M. Yousif  
Jozsef Duhl

Internal Medicine Residency Program, Raritan Bay Medical Center, Perth Amboy, N.J., USA

## Key Words

Cystic neoplasm · Pancreas · Erythropoietin · Biomarker

## Abstract

Cystic lesions of the pancreas are more frequently recognized due to the widespread use of improved imaging techniques. There are a variety of pancreatic cystic lesions with different clinical presentations and malignant potentials, and their management depends on the type of the cysts. Although the early recognition of a cystic neoplasm with malignant potential provides an opportunity of early surgical treatment, the precise diagnosis of the cystic neoplasm can be a challenge, largely due to the lack of reliable biomarkers of malignant transformation. We report a case of a large, multicystic neoplasm within the body and tail of the pancreas complicated by elevated erythropoietin, which is likely related to the malignant transformation of the pancreatic neoplasm.

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## Introduction

Cystic pancreatic lesions do not only have diverse histologic and imaging characteristics but also differ in clinical presentation and malignant potential [1]. The prevalence and size of the cystic lesions increase with age [2], and about 60% of cystic pancreatic neoplasms are malignant in individuals older than 70 years [3]. Generally, surgery is indicated for mucinous cystic neoplasms, intraductal papillary mucinous neoplasms, and solid pseudopapillary neoplasms that have a malignant potential [1]. Since the risk-to-benefit ratio might be high in

patients at a high risk for surgical resection, accurate preoperative risk stratification and decisions on operation versus observation require a precise characterization and diagnosis of the cystic lesion.

However, different cystic pathologies may have overlapping presentations [3]; the sensitivity and specificity of imaging studies or cyst aspiration are insufficient to accurately differentiate among benign, premalignant, and malignant pancreatic cystic lesions [4]. In addition, aspiration carries the risk of spilling malignant cells and reducing survival. Therefore, the discovery of tumor markers to differentiate benign, premalignant, and malignant cystic lesions would facilitate the diagnosis and decision-making process.

### Case Description

An 87-year-old female presented with fever, abdominal discomfort, poor oral intake, vomiting, and generalized weakness lasting for 2 days in 2011. She was found to have paroxysmal supraventricular tachycardia with a heart rate ranging from 110 to 240 beats per minute and was hypotensive. The arrhythmia was resistant to adenosine but responded to electrical cardioversion.

Her past medical history was significant for hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease, congestive heart failure, multiple lacunar stroke, hypothyroidism, and a pancreatic mass that had been detected 4 years ago and left without further investigation because the patient had refused treatment. There was no documented pancreatitis.

Abdominal CT demonstrated a multicystic mass in the body and tail of the pancreas as well as a mesenteric venous thrombus. A CT angiogram of the chest showed a bilateral pulmonary embolism. The cystic mass increased in size as shown on the CT scan, with the largest cyst growing from 2.5 cm in 2011 to 3.8 cm in 2013 (fig. 1b2, c2). The CT scan did not show any significant focal abnormality demonstrated in the abdominal and pelvic organs, except for the atrophic changes in the uterus and kidneys as well as a calculus in the left renal pelvis. Deep venous thrombosis was detected in the left femoral and popliteal veins. An echocardiogram showed normal structure and function of the left ventricle. The laboratory test showed an elevation in CA 19-9 in 2006 and erythropoietin (EPO) in 2014 (table 1). The tests mentioned above were performed in 2013, if not otherwise specified.

### Discussion

Cystic lesions of the pancreas present with diverse histological and imaging features, clinical presentations, and malignant potentials. Pancreatic cysts may be broadly classified into nonneoplastic, cystic neoplasms, and necrotic degeneration of solid tumors. Cystic neoplasms can be further categorized into serous cystadenoma (SCA), mucinous cystic neoplasms, intraductal papillary mucinous neoplasms, and solid pseudopapillary neoplasms [1]. We report a case of a slow-growing complex multicystic neoplasm that extensively occupied the body and tail of the pancreas and, more interestingly, was associated with an elevated EPO level.

In order to accurately categorize pancreatic cysts, information from a variety of sources, including history, radiography, and laboratory tests, is needed [5, 6]. As described above, the multicysts (>6), lobulated outlines, and central calcification (fig. 1) suggest an SCA of the pancreas (table 2). Furthermore, the existence of a large cyst (>2 cm) suggests a macrocystic

variant of SCA, which is very uncommon. Although the malignant potential of SCA is traditionally regarded as low [4], few cases of malignant SCA have been reported. Therefore, the potential for malignant growth of SCA does exist [7, 8]. In addition, the less dramatic elevation in CA 19-9 in 2006 may indicate the development of a small pancreatic malignancy, although CA 19-9 may also increase in other benign or malignant conditions [9]. Furthermore, the progressive decrease in the lipase levels indicates a permanent loss of lipase-producing cells in the pancreas likely secondary to the expansion of the neoplasm (table 1).

Interestingly, an elevation in the EPO level was revealed in this case. EPO is a glycoprotein mainly synthesized by peritubular fibroblasts in the renal cortex. Ectopic EPO is produced in various neoplasms arising in the kidney, liver, and cerebellum, which are physiological sites of EPO production. Those neoplasms include renal cell carcinomas, nephroblastomas, liver cell carcinomas, cerebellar hemangioblastomas, uterine fibroids, pheochromocytomas, and ovarian and hepatic cancers [10]. EPO was also found in metastatic pancreatic carcinoid tumor [11] and pancreatic ductal adenocarcinoma [12]. EPO was reported to exert antiapoptotic, anti-inflammatory, proliferative, and angiogenic effects on islet cells [13]. Moreover, EPO receptors are expressed in pancreatic tissue [14]. These features of EPO and its receptors may contribute to the neoplastic growth of pancreatic tissue as well as the invasiveness of pancreatic tumors. In the absence of other possible resources of EPO in this case, it is reasonable to presume that the elevated EPO was due to the enlarging pancreatic neoplasm, especially the malignant transformation. The relationship between EPO and pancreatic neoplasm is unclear, and further investigation is needed to clarify its function in the development and growth and its possible role as a biomarker of the malignant transformation of pancreatic neoplasms.

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### Disclosure Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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**Table 1.** Laboratory results

|                  | Value (year) | Normal ranges |
|------------------|--------------|---------------|
| Hemoglobin, g/dl | 10.8 (2014)  | 10.3–15.1     |
| Hematocrit, %    | 34.6         | 31.2–45.4     |
| EPO, IU/ml       | 43 (2014)    | 2.6–18.5      |
| CA 19-9, U/ml    | 44 (2006)    | 0–37          |
| Lipase, U/l      | 17 (2007)    | 13–60         |
|                  | 12 (2013)    |               |

**Table 2.** Characteristics of neoplastic pancreatic cysts [4, 6]

|               | SCA  | MCN  | IPMN   | SPN                   |
|---------------|--|--|--|-----------------------|
| Age, years    | 60–70  | 40–50  | 60–70  | 20–40                 |
| Gender        | F > M  | F > M  | F = M  | F > M                 |
| Site          | Head, body, tail   | Body, tail   | Head, body, tail   | Body, tail            |
| Morphology    | Typical: loculated, microcystic (>6, each <2 cm), honeycomb<br>Less common: macro-/oligocystic | Macrocytic (<6, each >2 cm), possible septations and wall calcifications | Dilated main pancreatic duct or pancreatic duct branches | Solid and cystic mass |
| Calcification | Central  | Peripheral   | Uncommon   | Uncommon              |

MCN = Mucinous cystic neoplasm; IPMN = intraductal papillary mucinous neoplasm; SPN = solid pseudopapillary neoplasm.



**Fig. 1.** Multiple cysts in the body and tail of the pancreas. **a1, a2** Multiple cysts in the body and tail of the pancreas demonstrated on different CT scan sections without contrast in 2007. The dotted circle shows the cystic mass with central calcification (arrow) and lobulated outline. **b1, b2** Pancreatic cysts on CT scan with contrast. The asterisk indicates the largest cyst with a diameter of 2.5 cm. **c1, c2** CT scan with contrast again showed an enlarged multicystic neoplasm in 2013, with the largest one measuring 3.8 cm in diameter (asterisk).